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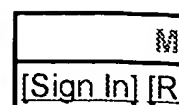
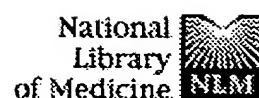
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A ligand-gated association between cytoplasmic domains of UNC5 and DCC family receptors converts netrin-induced growth cone attraction to repulsion.

Hong K, Hinck L, Nishiyama M, Poo MM, Tessier-Lavigne M, Stein E.

Department of Biology, University of California, San Diego 92093, USA.

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Netrins are bifunctional: they attract some axons and repel others. Netrin receptors of the Deleted in Colorectal Cancer (DCC) family are implicated in attraction and those of the UNC5 family in repulsion, but genetic evidence also suggests involvement of the DCC protein UNC-40 in some cases of repulsion. To test whether these proteins form a receptor complex for repulsion, we studied the attractive responses of *Xenopus* spinal axons to netrin-1, which are mediated by DCC. We show that attraction is converted to repulsion by expression of UNC5 proteins in these cells, that this repulsion requires DCC function, that the UNC5 cytoplasmic domain is sufficient to effect the conversion, and that repulsion can be initiated

netrin-1 binding to either UNC5 or DCC. The isolated cytoplasmic domains of DCC and UNC5 proteins interact directly, but this interaction is repressed in the context of full-length proteins. We provide evidence that netrin-1 triggers the formation of a receptor complex of DCC and UNC5 proteins and simultaneously derepresses the interaction between the cytoplasmic domains, thereby converting DCC-mediated attraction to UNC5/DCC-mediated repulsion.

PMID: 10399920 [PubMed - indexed for MEDLINE]

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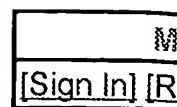
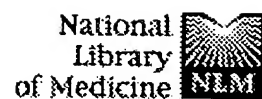
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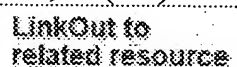
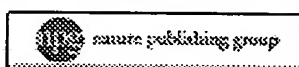
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Netrin-1 acts as a survival factor via its receptor UNC5H and DCC.

Llambi F, Causeret F, Bloch-Gallego E, Mehlen P.

Apoptosis/Differentiation Laboratory-label La Ligue, Mo and Cellular Genetic Center, CNRS UMR 5534, Universi Lyon, 69622 Villeurbanne, France.

The membrane receptors DCC and UNC5H have been shown to be crucial for axon guidance and neuronal migration by acting as receptors for netrin-1. DCC has also been proposed as a dependence receptor inducing apoptosis in cells that are dependent on netrin-1 availability. Here we show that the netrin-1 receptors UNC5H (UNC5H1, UNC5H2, UNC5H3) also act as dependence receptors. UNC5H receptors induce apoptosis, and this effect is blocked in the presence of netrin-1. Moreover, we demonstrate that UNC5H receptors are cleaved in vitro by caspase in their intracellular domains. This cleavage may be the result of the exposure of a fragment encompassing a death domain required for cell death induction in vivo. Finally, we present evidence that during development of the nervous system, the presence of netrin-1 is crucial to maintain survival of UNC5H and DCC-expressing neurons, especially in the ventricular zone of the brainstem. Altogether, these results argue for a role

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netrin-1 during the development of the nervous system, not as a guidance cue but as a survival factor via its receptors and UNC5H.

PMID: 11387206 [PubMed - indexed for MEDLINE]

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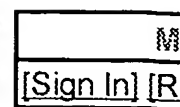
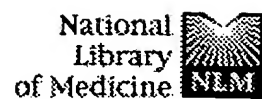
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Cloning of three mouse *Unc5* genes and their expression patterns at mid-gestation.

Engelkamp D.

Max Planck Institute for Brain Research, Deutschordenstr 46, 60528 Frankfurt, Germany. d.engelkamp@mpih-frankfurt.mpg.de

The *Caenorhabditis elegans* gene *unc-5* and its vertebrate homologues are Netrin receptors. In this study, I report the cloning of three mouse *Unc5* family members, namely, *Unc5h2* and *Unc5h4*. Furthermore, a comparative expression analysis is presented with *Unc5h3*, deleted in colorectal cancer, and *Netrin-1*. Transcript distribution is studied during early development, mammary bud formation, vascularisation, and limb development. The most widely expressed *Unc5* family member is *Unc5h2* and its mRNA is observed during early blood vessel formation, in the semicircular canal and in a ventral to dorsal gradient in the retina. *Unc5h1* expression is restricted to the central nervous system, whereas, sites of *Unc5h4* expression are in the developing limb and mammary gland.

PMID: 12351186 [PubMed - indexed for MEDLINE]

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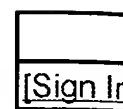
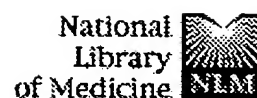
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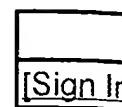
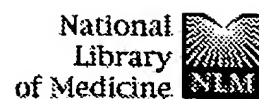
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








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
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
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
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
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












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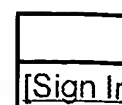
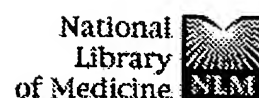
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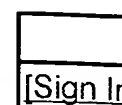
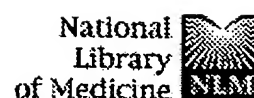
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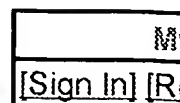
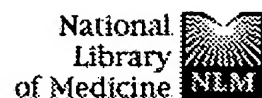
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Guidance of developing axons by netrin-1 and its receptors.

Leonardo ED, Hinck L, Masu M, Keino-Masu K, Faze Stoeckli ET, Ackerman SL, Weinberg RA, Tessier-Lavigne M.

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PMID: 9598381 [PubMed - indexed for MEDLINE]

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Vertebrate homologues of *C. elegans* UNC-5 are candidate netrin receptors.

Leonardo ED, Hinck L, Masu M, Keino-Masu K, Ackermann SL, Tessier-Lavigne M.

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In the developing nervous system, migrating cells and axons are guided to their targets by cues in the extracellular environment. The netrins are a family of phylogenetically conserved guidance cues that can function as diffusible attractants and repellel different classes of cells and axons. In vertebrates, insects and nematodes, members of the DCC subfamily of the immunoglobulin superfamily have been implicated as receptors that are involved in migration towards netrin sources. The mechanisms that direct migration away from netrin sources (presumed repulsions) are less well understood. In *Caenorhabditis elegans*, the transmembrane protein UNC-5 (UNC-54) has been implicated in these responses, as loss of unc-5 function causes migration defects and ectopic expression of unc-5 in some neurons can redirect their axons away from netrin source. Whether UNC-5 is a netrin receptor or simply

accessory to such a receptor has not, however, been defined. We now report the identification of two vertebrate homologues of UNC-5 which, with UNC-5 and the product of the mouse cerebellar malformation gene (rcm), define a new subfamily in the immunoglobulin superfamily, and whose messenger RNAs show prominent expression in various classes of different neurons. We provide evidence that these two UNC-5 homologues, as well as the rcm gene product, are netrin-binding proteins, supporting the hypothesis that UNC-5 and its relatives are netrin receptors.

PMID: 9126742 [PubMed - indexed for MEDLINE]

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